REMARKS

Applicant acknowledges receipt of the Office Action mailed November 14, 2005.

All of the amendments to the claims are supported by the application, as originally filed.

The Title of the Application is amended herein to reflect more appropriately the presently claimed invention.

Claims 1, 3-5, 7, 9, 19, 32, 35, and 38-39 are amended herein, and Claims 33-34 and 36-37 are canceled herein. Claims 1-7, 9, 19, 32, 35 and 38-43 will be pending following entry of this Amendment. No new matter is being added by the amendments made herein.

Entry of this Response is respectfully requested.

The Written Description Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 9, 19 and 32-43

Claims 1-7, 9, 19 and 32-43 have been rejected as failing to comply with the written description requirement of § 112 over the recitation of, "wherein no portion of said surface of said solid support is excluded from occupation by an immobilized oligonucleotide, said device having been manufactured by a process comprising immersion of said surface in a liquid composition comprising immobilizable oligonucleotide primers." Applicant notes that the rejection of Claims 33-34 and 36-37 is no longer relevant because those claims have been canceled from the Application. The language which served as the basis for the rejection has been deleted from the claims, thereby obviating the

written description rejection of pending Claims 1-7, 9, 19, 32, 35 and 38-43. Accordingly, withdrawal of the written description rejection of these claims is requested.

Claims 32-37

Claims 32-37 have been rejected as failing to comply with the written description requirement over the recitation of "said plurality of species of labeled hybridization probes that comprise no more than two species of labeled hybridization probes." The Examiner stated:

> "[t]his limitation encompasses no more than a single species of hybridization probes, explicitly claimed in Claim 33, for which there is no support in the Specification. Applicant cites Example 9 as providing support for the limitation of no more than a single probe. However, in this example there are two molecular beacon probes arrayed, one of SEQ ID NO:7 and one of SEQ ID NO:5 (page 46, lines 25-30, page 47, lines 1-20)."

Thus, the rejection of Claim 32 and all claims depending therefrom is based on the notion that Claim 32 embraces unsupported subject matter. Applicant notes that the rejection of Claims 33-34 and 36-37 is no longer relevant because those claims have been canceled from the Application.

The amended claims comply with the written description requirement of § 112. The Specification describes in the paragraph bridging pages 10-11 different features of the invention, including nucleic acid amplification reactions conducted in contact with a solid support comprising immobilized oligonucleotides. This section of the Specification states:

> "Herein there are disclosed methods of making and using ***devices for conducting nucleic acid amplification reactions***. The invention particularly embraces methods of manufacturing which

> optionally may employ, but are not limited to, the immobilization chemistries described below. In accordance with certain embodiments, a nucleic acid amplification reaction is conducted in contact with ***a solid support having disposed thereon at least one species of immobilized amplification primer.*** In a preferred embodiment, the immobilized amplification primer is one member of a pair of oppositely disposed oligonucleotides, one each being complementary to opposite strands of the target nucleic acid that is to be amplified. The primers are oriented such that the extension product of a first primer can serve as the template for hybridization and extension of the opposite strand primer. In another embodiment, ***there is immobilized to the same solid support at least one probe for detecting amplicons generated using the immobilized amplification primers.*** In highly preferred embodiments, the probe is a self-reporting probe such a molecular torch or molecular beacon. Manufacturing of the device advantageously eliminates the need for maintaining spatial separation between the immobilized probes and primers, and so greatly simplifies unit construction." [Emphasis added]

This excerpt provides written description support for devices comprising a solid support, at least one immobilized amplification primer, and at least one immobilized probe, as recited in amended Claim 1. The limitations of Claim 1 are incorporated into pending Claims 32 and 35 by virtue of their dependency, whether direct or indirect, on Claim 1. In view of the present amendments, pending Claims 32 and 35 embrace devices comprising "at least one" but not more than two species of labeled hybridization probe, and are presented as complying with the written description requirement. Accordingly, withdrawal of the written description rejection of pending Claims 32 and 35 is requested.

The Rejection Under § 112, Second Paragraph

Claims 1-7, 9, 19 and 32-43

Claims 1-7, 9, 19 and 32-43 have been rejected as being indefinite because Claim 1 recited

"wherein no portion of said surface of said solid support is excluded from occupation by an immobilized oligonucleotide, said device having been manufactured by a process comprising immersion of said surface in a liquid composition comprising immobilizable oligonucleotide primers." Applicant notes that the rejection of Claims 33-34 and 36-37 is no longer relevant because those claims have been canceled from the Application. The language which served as the basis for the rejection has been deleted from the claims, thereby obviating the rejection of pending Claims 1-7, 9, 19, 32, 35 and 38-43 under § 112, second paragraph. Accordingly, withdrawal of the rejection is requested.

Claims 32-38

Claims 32-38 have been rejected over the recitation of "said plurality of species of labeled hybridization probes that comprises no more than two species of labeled hybridization probes" (Claim 32), "said plurality of species of labeled hybridization probes that comprises no more than two species of labeled hybridization probes comprises no more than a single species of labeled hybridization probe" (Claim 33), "said plurality of species of amplification primer that comprises no more than a single species of amplification primer" (Claims 34-35 and 38). More specifically, the Examiner pointed out that the word "plurality" refers to at least two of something, and so it was unclear how the claims could embrace fewer than two of that thing.

The claims have been amended to comply with the requirements under § 112, second paragraph. Applicant notes that the rejection of Claims 33-34 and 36-37 is no longer relevant because those claims have been canceled from the Application. The language which served as the basis for the rejection has been deleted from the claims and replaced by "at least one." Support for the amended claim language has been given hereinabove. Applicant notes that Claim 39, although not identified in the rejection, has been amended in parallel to recite "at least one" instead of "plurality." Accordingly, pending Claims 32 and 35 are presented as being clear and definite, and so withdrawal of the rejection

under § 112, second paragraph is requested.

The Rejection Under § 102(b)

Claims 1-7, 9, 32-35 and 37-42 have been rejected under 35 U.S.C. § 102(b) as anticipated by a published PCT Application naming Brennan et al., as inventors ("**Brennan**" hereafter). The Office Action indicated on page 16 under § 21 that **Brennan** failed to instruct beads as solid supports, and the "bead" limitation of Claim 36 rendered that claim outside the § 102(b) rejection. Applicant notes that the rejection of Claims 33-34 and 36-37 is no longer relevant because those claims have been canceled from the Application.

The claims have been amended to overcome the rejection under § 102(b). More particularly, the limitation of Claim 36 has been incorporated into amended Claim 1, and Claim 36 has been canceled. Claim 37 has additionally been canceled because the "planar surface" limitation recited therein is no longer embraced by the independent claim. Since **Brennan** does not disclose the "bead" limitation which is incorporated into all of the instant claims by virtue of depending directly or indirectly on amended Claim 1, all of the pending claims are novel in light of the **Brennan** reference. Accordingly, withdrawal of the rejection under § 102(b) is requested.

The Rejections Under § 103(a)

I. The Rejection of Claim 19 Under § 103(a)

Claim 19 has been rejected under 35 U.S.C. § 103(a) as unpatentable over the combined disclosure of **Brennan**, Hu et al., (WO 01/48242) ("**Hu**" hereafter), and a section from the **1988 Stratagene Catalog**. More particularly, the Office Action expresses that it would have been obvious

for one of ordinary skill in the art to have packaged the device of **Brennan** into a kit, as suggested by **Hu**, and as motivated by the disclosure contained in the **1988 Stratagene Catalog**. The rejection is based on the premise that the invention defined by Claim 1 is anticipated by **Brennan**.

To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. (M.P.E.P. § 2143.03) The combined disclosure of **Brennan**, **Hu** and the **Stratagene Catalog** fails to instruct the use of beads (*i.e.*, microparticles) as solid supports, as recited in amended Claim 1. In light of this fact, Claim 19, which depends from Claim 1, cannot be considered obvious under § 103(a). Accordingly, withdrawal of the rejection of Claim 19 under § 103(a) is requested.

II. The Rejection of Claim 36 Under § 103(a)

Claim 36 has been rejected under 35 U.S.C. § 103(a) in view of the combined disclosure of **Brennan** and **Lund** (*Nucl. Acids Res.*, **16**: 10861-10880 (1988)). The Office Action indicates that **Brennan** fails to disclose beads for use as solid supports in the array assembly technique, but that **Lund** teaches DNA probes immobilized on beads. According to the rejection, it would have been *prima facie* obvious for one of ordinary skill to have substituted the beads taught by **Lund** as solid supports in the device of **Brennan**, because **Lund** teaches that particles (*i.e.*, beads) offer certain advantages over membrane filters when used in mixed phase hybridization reactions, have large surface areas for DNA attachment, and can avoid the use of a centrifuge. Applicant notes that the limitation of canceled Claim 36, which originally depended from Claim 1, has been incorporated into Claim 1. Accordingly, the instant response is relevant to amended Claim 1.

Reasons why the invention defined by amended Claim 1 cannot be considered *prima facie* obvious over the cited combination of references are presented below.

A. The Suggested Modification Changes the Principle of Operation of the Invention Disclosed in the Primary Reference

Brennan instructs a combinatorial approach for conducting large numbers of independent reactions, such as polynucleotide amplification reactions, in parallel with each other using an "array assembly" technique (*see* Abstract; final paragraph of Background; second paragraph of Detailed Description, etc.). The only structures taught for practicing the disclosed method are "surface tension arrays" (*see* page 5 at lines 11-12), which "comprise patterned hydrophilic and hydrophobic sites" (*see* page 19 at lines 16-17) arranged on substantially planar solid supports. Referring to surface tension arrays, **Brennan** instructs that (*see* page 19 at lines 23-25), "a hydrophilic site is spatially segregated from neighboring hydrophilic sites because of the hydrophobic sites between hydrophilic sites." **Brennen** further instructs that the "hydrophilic sites are derivatized sites" (*see* page 21 at line 3), and that the hydrophobic sites serve to maintain spatial separation between different reactions taking place in contact with the surface of the solid support (*see* page 19 at lines 31-32). The physical arrangement of reactant-containing hydrophilic sites and hydrophobic sites is illustrated in Figure 2, and chemical derivatization and photomasking techniques that can be used to create patterned distributions of hydrophobic and hydrophilic areas are discussed, for example, on page 21 at line 10 and extending to page 22 at line 9. **Brennan** emphasizes the practical value of this arrangement in connection with practice of the disclosed technique in the paragraph bridging pages 20-21, where it is stated, "[f]or a patterned array where the polar synthesis regions (hydrophilic sites) are separated by nonpolar regions (hydrophobic sites), droplets of liquid are confined to a particular synthesis site, and will not migrate to an adjacent site because of the surface tension difference imposed by the nonpolar mask." Thus, the primary prior art reference instructs a solid support divided into separate areas by hydrophobic partitions which serve the same purpose as the walls between wells in a microtiter plate (*see* the Office Action, last paragraph of page 5 referencing **Brennan** page 19 at lines 23-25).

Lund teaches covalent attachment of DNA or oligonucleotides to magnetic beads (*see* Abstract). **Lund** illustrates the disclosed method by attaching DNA to beads, and then using the derivatized beads in procedures involving hybridization to complementary nucleic acids. This hybridization involving probe-beads (*see* page 10866) was accomplished by combining the probe-beads with a target nucleic acid in a hybridization solution. **Lund** does not teach or suggest partitioning of a bead surface to create separate areas capable of isolating different reactions. Instead, **Lund** describes hybridizing the probe-beads in a bulk hybridization solution such that a target molecule would be able to contact any probe immobilized on the bead surface. One would readily accept that all oligonucleotides disposed on bead surface would be in fluid communication with each other during the intended use of the probe-beads taught by **Lund**.

It would not have been obvious for an ordinary skilled artisan to have substituted the beads of **Lund** for the planar support of **Brenann** as outlined in the § 103(a) rejection, because doing so would substantially change the principle of operation underlying the device taught by the primary prior art reference. The benefit of the device disclosed by **Brennan** depends on the ability to perform large numbers of amplification reactions in parallel with each other on a solid support. Critical to this ability is maintenance of spatial separation between different reactions carried out on different areas of the solid support. Thus, successful use of the device taught by **Brennan** requires that different reactions comprising immobilized oligonucleotides are not in fluid communication with each other. Eliminating the hydrophobic barriers which maintain the reactions independent of each other, as would be the case for the suggested obvious device of **Brennan** in view of **Lund**, would allow mixing of the constituents for the different reaction, and so would compromise the intended purpose of the array assembly technique. Since all oligonucleotides immobilized on the surface of a bead-based device in accordance with **Brennan** in view of **Lund** must necessarily be in fluid communication with each other during their intended use, and since the suggested obvious device would sacrifice features which are critical for the principle of operation underlying the device of **Brennan**, the suggested modification inappropriately

changes the principle of operation underlying the device taught by the primary prior art reference.

As articulated under M.P.E.P. § 2143.01, "[i]f the modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." The principle of operation of the "array assembly" technique taught by **Brennan** (*i.e.*, involves bringing two arrays into apposition) depends on multiple independent reactions taking place on the assembled solid support. Immobilizing oligonucleotides onto the surface of a bead in accordance with the suggested obvious device of **Brennan** in view of **Lund** would eliminate the ability to maintain spatial separation between different reactions taking place on the bead, and so would not facilitate carrying out large numbers of independent reactions on a unitary solid support. Because the principle of operation underlying the prior art invention being modified must be fundamentally changed to result in the suggested obvious device, the case for *prima facie* obviousness of the instantly claimed invention should not be maintained. Accordingly, withdrawal of the § 103(a) rejection of previously presented Claim 36, now canceled and redrafted as Claim 1, is requested.

B. Absence of Spatial Separation Between Independent Reactions on a Bead Surface Voids the Need for Indexing by Immobilization

Brennan instructs immobilization of oligonucleotides and other reactants as a means for spatially indexing large numbers of different reactions performed using the disclosed array assembly technique. For example, referring particularly to polynucleotide amplification reactions, **Brennan** states (*see* page 36 at lines 13-16):

> "[w]ith the aid of arrays, large numbers of PCR reactions may be performed in parallel by confining selected PCR reactants to definite areas on two arrays, bringing two arrays into apposition, and allowing reactants on two arrays to merge and triggering PCR reactions."

Brennan describes fabrication of surface tension arrays on substantially planar solid supports, and indicates that such arrays typically comprise a minimum of 20-500 "derivatized sites" (*see* page 19 at lines 13-15). **Brennan** generally emphasizes maintaining the numerous reactions spatially separate from each other, and indicates on page 22 at lines 6-9:

> "[v]ariations of these procedures [for creating hydrophilic areas separated by hydrophobic partitions] may also be used to fabricate a solid support surface such that solution of reactants at a derivatized site is spatially separated from solution of reactants at other derivatized sites by surface tension. Separate reactions may be carried out at each derivatized site."

The reason for immobilizing oligonucleotides is made clear in the discussion of array fabrication (*see* page 19 at lines 23-26), where **Brennan** indicates that surface tension arrays comprise patterned hydrophillic and hydrophobic sites, and further that the hydrophilic sites are,

> "spatially segregated from neighboring hydrophilic sites because of the hydrophobic sites between the hydrophillic sites. *This spatially addressable pattern* enables the precise and reliable location of chemical or biological entities, such as molecules, cells, viruses, etc." [Emphasis added]

Thus, maintaining the spatial separation between different reactions on the solid support surface is critical to indexing the numerous different reactions described in the primary reference, and this, in turn, depends on confining reactants, such as by immobilization, to definite areas on the arrays.

Lund teaches bead-based immobilization of nucleic acids for use as hybridization probes, but says nothing about how one would create multiple areas for isolating one type of reaction from another on the surface of a single bead. To maintain a single type of reaction isolated from others using a device in accordance with **Brennan** in view of **Lund**, it would be necessary to limit the number of reactions on

the bead to only a single type of reaction, thereby compromising the objective of **Brennan** to be able to conduct large numbers of reactions in parallel by array assembly.

Absent a need for monitoring the locations of large numbers of different reactions on a bead surface, there would be no reason for immobilizing the oligonucleotide reactants required by the instant claims. If a device in accordance with **Brennan** in view of **Lund** is intended somehow to resemble a unit cell of the device described by **Brennan** (*i.e.*, so that a single type of reaction takes place on the bead surface), then there would be no motivation for immobilizing both primers and probes since indexing different reactions by spatial separation, which was the reason for **Brennan** to immobilize reactants, would be unnecessary. Moreover, since **Brennan** actually instructs (*see* page 18 at lines 16-21) initiating amplification reactions by first releasing immobilized primers, and since the skilled artisan would have no reason for indexing primers by immobilization only to release them, it seems more likely that soluble primers would have been employed in the first place. Despite the fact that derivatized beads according to **Lund** can provide certain advantages over other types of solid supports (*i.e.*, membrane filters) used in hybridization procedures, those advantages are lost when the intended use of the immobilized primers requires release from the solid support. Thus, the suggested obvious device of **Brennan** in view of **Lund** would lack the ability to maintain separate reactions on the bead surface, and so would void the need for immobilizing both primers and probes. Without a need, it would not be obvious to immobilize primers onto a probe-bead to create the suggested obvious device. Accordingly, withdrawal of the § 103(a) rejection of previously presented Claim 36, now canceled and redrafted as Claim 1, is requested.

III. The Rejection of Claim 43 Under § 103(a)

Claim 43 has been rejected under 35 U.S.C. § 103(a) as unpatentable over the combined disclosure of **Brennan** and **Gerard** et al., (*Mol. Biotech.*, **8**:61-77 (1997)). More particularly, the

Office Action indicates that **Brennan** discloses all elements of previously presented Claim 43, except for an MMLV reverse transcriptase enzyme, and that **Gerard** discloses an MMLV reverse transcriptase enzyme lacking RNase H activity. According to the rejection, it would have been *prima facie* obvious to one of ordinary skill in the art to have used the MMLV enzyme of **Gerard** in the liquid composition of **Brennan** to result in the invention of Claim 43.

To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. (M.P.E.P. § 2143.03) The combined disclosure of **Brennan** and **Gerard** fails to instruct the use of beads (*i.e.*, microparticles) as solid supports, as recited in amended Claim 1. In light of this fact, Claim 43, which depends ultimately from Claim 1, cannot be considered obvious under § 103(a). Accordingly, withdrawal of the rejection of Claim 43 under § 103(a) is requested.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

Deposit Account Information

Please charge any fees due in connection with this Reply, including the fee for a three-month extension of time, to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

Appl. Serial No. : 10/621,803
Amendment dated May 10, 2006
Reply to Office Action of November 14, 2005

Certificate of Transmission

I hereby certify that this correspondence is being sent by facsimile to (571) 273-8300 on the date indicated below to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Respectfully submitted,
GEN-PROBE INCORPORATED

Dated: May 10, 2006

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